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IMMUNOSTIMULATOR
[Meneki fukatuzai]

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Claim

An immunostimulator for acquired immune deficiency syndrome virus-infected patients characterized by comprising a Chinese medicine formulation, "Shosaikotou" [transliteration].

Detailed explanation of the invention

Industrial application field

The present pertains to an immunostimulator for acquired immune deficiency syndrome virus-infected patients.

Prior art

Acquired immune deficiency syndrome (AIDS) is induced as a result of acquired immune deficiency syndrome viral infection. It is a disease with critical cellular immunodeficiency as a main symptom. This disease has become a social issue because of no complete cure has been established yet, and at the same time, the fatality rate is extremely high.

As a drug currently available for treating AIDS, there are antiviral drugs such as azidothymidine (AZT), etc. and immunostimulators such as interleukin-2, interloin [sic]-γ, etc., but the treatment effects of those drugs are not necessarily decisive, and the development of an effective drug for treating AIDS has been desired.

Problem to be solved by the invention

This invention is to provide an immunostimulator for human immunodeficiency virus-infected patients for the purpose of treating AIDS.

Means to solve the problem

The inventors of this invention carried out studies to activate the immune system of HIV-infected AIDS patients with various Chinese medicine formulations, and as a result, they found that the immune stimulation activity for AIDS virus-infection patients was observable in a Chinese medicine formulation comprising *Radix Bupleuri, Scutellaria baicalensis Georgi, Radix Glycyrrhizae, Zingseng Radix, Zingiberis Rhizoma, Zizyphi Fructus* and *Cortex Eucommiae*, that is, a Chinese medicine formulation called Shosaikotou. This invention is based on this finding, and it is an immunostimulator for AIDS virus infection patients comprising Shosaikotou. For Shosaikotou, the crude drugs contained, amount, extraction method, etc., are described in the Chinese medicine classical scriptures ("Shokanron" and "Kinkyouryaku"), the prescription has been known to be usable to treat various diseases such as hepatic function disorders, chronic gastrointestinal disorders, poor postpartum recovery, etc. and has an immune stimulation action in cancer patients, but the function stimulating the immune system of AIDS virus infected patents has been completely unknown previously.

The specific type of Shosaikotou is not especially restricted, and any Shosaikotou prescription prepared according to the compounding proportions of the crude drug components along the descriptions in the Chinese medicine classical scriptures such as Shokanron, Kinkyouryaku, etc., is suitable for use.

A preferable specific example of respective proportions of the crude drug components of Shosaikotou comprises 4-7 parts by weight of *Radix Bupleuri*, 3 parts by weight of *Scutellaria baicalensis Georgi*, 2 parts by weight of *Radix Glycyrrhiza*, 2-3 parts by weight of *Zingseng Radix*, 1 part by weight of *Zingiberis Rhizoma*, 2-3 parts by weight of *Zizyphi Fructus* and 4-5 parts by weight of *Cortex Eucommiae*.

Another specific example of Shosaikotou may be prepared as a Chinese medicine drug extract formulation by brewing 7 g of *Radix Bupleuri*, 3 g of *Scutellaria baicalensis Georgi*, 2 g of *Radix Glycyrrhiza*, 3 g of *ZingsengRadix*, 1 g of *Zingiberis Rhizoma*, 3 g of *Zizyphi Fructus* and 5 g of *Cortex Eucommiae* with 600 mL of water to 350 mL, skimming the scum and reducing the solution to 200 mL. This solution may be taken as an immunostimulator in 3 portions, but considering the ease of taking and portability, it may be prepared as an immunostimulator in the form of dried extract powder or extract formulation.

Especially, a Shosaikotou product prepared according to the following procedures is preferable with respect to the pharmacological effect expected to be exhibited.

According to Shokanron or Kinkyouryaku, 7 g of *Radix Bupleuri*, 3 g of *Scutellaria baicalensis Georgi*, 2 g of *Radix Glycyrrhiza*, 3 g of *ZingsengRadix*, 1 g of *Zingiberis Rhizoma*, 3 g of *Zizyphi Fructus* and 5 g of *Cortex Eucommiae* are mixed with 10-12 times the amount of pure water, and extraction is carried out at 955 [sic] - 100°C for 60 min. After extraction, the solids content is removed, the liquid isolated is spray-dried to obtain a dried powder of Shosaikotou extract (4.5 g of dried extract powder contains 25.0-52.0 mg of glycyrrhizin, 90-210 mg of baicalin and 2.3-6.9 mg of saikosaponin b_2).

The formulation may be carried out with conventional procedures by adding suitable excipients, auxiliary components, etc., used for conventional formulation procedures to the dried extract powder prepared as described above to prepare formulation forms such as powder, granules, tablet, capsule, etc.

A specific example of the production of the immunostimulator of this invention is shown as follows.

Specific Example 1

To 7 g of *Radix Bupleuri*, 3 g of *Scutellaria baicalensis Georgi*, 2 g of *Radix Glycyrrhiza*, 3 g of *ZingsengRadix*, 1 g of *Zingiberis Rhizoma*, 3 g of *Zizyphi Fructus* and 5 g of *Cortex Eucommiae*, 300 mL of pure water was added, and extraction was carried out at 100°C for 60 min. After extraction, the liquid-solid separation was carried out with centrifugation, the solution separated was spray-dried at a temperature below 50°C to obtain a dried extract powder of Shosaikotou. The components in 4.5 g of the dried extract powder prepared were quantitatively determined to be 42.5 mg of glycyrrhizin, 160 mg of baicalin and 4.5 mg of saikosaponin b_2.

Effect of the invention

The immunostimulator of this invention having an immune stimulation effect on AIDS virus infected patients is explained with experimental examples as follows.

Experimental Example 1

The extract powder prepared in the above Specific Example 1, 4.5 g per day was administered in 3 doses a day for 3 months to a hemophiliac patient who was an AIDS virus infected patient as a result of transfusion of a contaminated blood formulation. Before administration, 1, 2, 3 and 6 months after administration, measurements were carried out for leukocyte count, lymphocyte count, helper T-cell (OKT4) count, suppressor T-cell (OKT8) count, OKT4/OKT8 ratio and two-color analysis value change.

As a result, the OKT4/OKT8 ratio being 0.37 before administration was increased to 0.55 after 6 months of administration, and the OKT8 count was reduced to 390/μL from 649/μL.

Experimental Example 2

The extract powder prepared in the above Specific Example 1, 4.5 g per day was administered in 3 doses a day for 3 months to 5 AIDS virus infected patients. Before administration, 1, 2 and 3 months after administration, measurements were carried out for leukocyte count, lymphocyte count, helper T-cell (OKT4) count, suppressor T-cell (OKT8) count, OKT4/OKT8 ratio and two-color analysis value change.

The results obtained are summarized in Table 1.

TABLE 1

リンパ球数増加	60%
OKT4数増加	80%
OKT8数増加	80%
OKT4/OKT8比増加	40%
トゥーカラー解析	
① $CD4^+2H4^+$値上昇	80%
$CD4^+2H4^-$値上昇	20%
$CD8^+CD11^+$値上昇	80%
$CD8^+CD11^-$値上昇	40%
$CD8^+HLA-DR^+$値上昇	60%
$Leu7^+CD16^+$値上昇	40%
$Leu7^+CD16^-$値上昇	60%

Key: 1 Lymphocyte count increase

OKT4 count increase

OKT8 count increase

OKT4/OKT8 ratio increase

Two-color analysis

$CD4^+2H4^+$ value elevation

$CD4^+2H4^-$ value elevation

$CD8^+2H11^+$ value elevation

$CD8^+2H11^-$ value elevation

$CD8^+HLA\text{-}DR^+$ value elevation

$Leu7^-CD16^+$ value elevation

$Leu7^+CD16^+$ value elevation

As apparent from those results shown in the table, the immunostimulator of this invention was confirmed to have an immune stimulation effect on AIDS virus infected patients.

Subsequently, an oral administration acute toxicity test was carried out for the immunostimulator of this invention with ddY male mice and Wistar male rats. As a result, the oral administration of the immunostimulator prepared in the Specific Example 1 even at a dose of 15 g/kg (maximum dose limit) showed no fatal case. Therefore, the toxicity of the immunostimulator of this invention was found to be low, and the safety was found to be high. Incidentally, Shosaikotou has been used clinically from ancient times to the present day, and it has been confirmed to have minimal adverse effects. The effective dose of the immunostimulator of this invention depends on the age of the patient, the bodyweight, and the seriousness of disease, etc., but considering the experimental data and result of the acute toxicity test obtained, the adult daily dose is generally in the range of 1-10 g of the dried extract powder, and depending on the symptoms observed, it may be administered suitably in 3 doses a day.

This invention is explained further in detail with application examples as follows, but this invention is not necessarily restricted by these examples.

Application Example 1

A mixture of 200 g of the dried extract powder prepared in Specific Example 1 described above with 89 g of lactose and magnesium stearate was pelletized to prepare a slag pellet of 20 mm diameter and about 2.3 g of weight, which was subsequently pulverized with an oscillator, the granules were classified and sieved to obtain a granular formulation of 20-50 mesh particles.

The granular formulation prepared is administered at a single dose in the range of 0.5-4.5 g (as dried extract powder of the immunostimulator of this invention), which is specifically determined depending on the symptoms observed, at a frequency of 3 times a day.

Application Example 2

A mixture of 200 g of the dried extract powder prepared in Specific Example 1 described above with 20 g of microcrystalline cellulose and 5 g of magnesium stearate was pelletized with a single-shot pelletizer to prepare a pellet of 7 mm diameter and about 225 mg of weight. The single pellet of the pellet formulation prepared contained 200 mg of the dried extract powder as the immunostimulator of this invention. Depending on the symptoms, 2-16 tablets are to be administered 3 times a day.

Application Example 3

A hard capsule was filled with 500 mg of the dried extract powder prepared in Specific Example 1 above. Depending on the symptoms, 2-20 capsules are to be administered 3 times a day.